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PALMER & DODGE, LLP
KATHLEEN M. WILLIAMS
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER	
SWITZER, JULIET CAROLINE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,518	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C: Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19-24,28,29,31,33,38,41,43,49 and 56-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19-24,28,29,31,33,38,41,43,49 and 56-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 10/1/07. Claims 39, 46, 54, and 55 were canceled. Claims 17, 19-21, 23-24, 28-29, 31, 33-34, 38, 41, 43, 49, and 56 and have been amended claims 57-61 have been added. Claims 17, 19-21, 23-24, 28-29, 31, 33-34, 38, 41, 43, 49, and 56-61 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not sufficient to place the claims in condition for allowance for the reasons set forth in this office action. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The declaration filed 10/1/07 has been considered and is fully addressed in the response to remarks section of this office action.

Priority

3. The claims have basis in parent applications 10/268730 and 09/477148, and thus have an effective filing date of at least 1/4/00, except for claims which are rejected in this office action for having new matter relative to the instant application. These claims do not have support in the parent.

4. The examiner was not able to identify basis in the provisional application 60/115,125 for the instantly claimed invention. For example, basis for the limitation that the blood samples have not been fractionated into cell types from subjects was not identified, nor basis for the current claims which recite analysis for each gene in a collection of two or more genes for the same disease, nor for quantifying a level of differential expression, nor for quantifying levels of

RNA in samples. If applicant desires priority to the provisional application for the pending claims, applicant should provide description of how each element of the pending claims is supported by the disclosure of the provisional application.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 20, 21, 23, 24, 28, 29, 31, 33, 34, 38, 41, 42, 49, 56, 57, 58, 59, 60, and 61are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

7. In claims 57 and 58, the limitation that the blood samples "comprise leukocytes which a have not been fractionated into cell types" is new matter. Such a recitation includes, for example, testing a blood sample where the red blood cells and the white blood cells have been separated, and also includes, the testing of whole blood RNA. There is clearly basis for the latter.

8. Applicant asserts in the remarks that this claim limitation finds clear support in the specification, including figure 5C which shows standardized fractions of leukocytes. However, these are not leukocytes that have not been fractionated into cell types, as they have clearly been fractionated into cell types. While RNA levels have been determined in each of the fractions,

this is not basis for the negative limitation "have not been fractionated into cell types." There is no discussion or example in the specification of the testing of RNA in blood samples which comprise leukocytes which have not been fractionated into cell types. Applicant has attempted to present a claim which excludes a particular process step from a method (that is, fractionating the leukocytes) and then provides basis for the exclusion of the step in a method where the opposite occurred. This is not sufficient basis for the claim limitation because there is nothing in the specification that suggests applicant contemplated the exclusion of a step of fractionating leukocytes into cell types. Therefore, claims 57 and 58, as well as all claims which depend from these are rejected for having new matter.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 17, 19-21, 23-24, 28-29, 31, 33-34, 38, 41, 49, 56, 57, 58, and 61 are rejected under 35 U.S.C. 102(b) and 102(a) as being anticipated by Ralph et al. (WO 98/24935).

11. Claims 17, 19-21, 23-24, 28-29, 31, 33-34, 38, 41, 49, 56, 57, 58 and 61 are rejected under 35 U.S.C. 102(e) as being anticipated by Ralph et al. (6190857).

12. ***Need to address claim 61 - evidence from unigene and sequence search or write 103 with Sharma and/or Ralph alone.

These references have substantially identical disclosures, but are applicable to the instantly claimed invention as of different dates. Both references are applied to the instant claims. In the rejection, column and line numbers from the issued patent are used to refer to the disclosure, but each portion referenced in the patent is also present in the WO document.

Ralph et al. teach that responses secondary to disease states may be reflected in changing patterns of leukocyte mRNA levels that correlate with the presence of the disease state (Col. 5, lines 27-33). Ralph et al. teach the use of RT-PCR to identify two or more markers useful for diagnosing a disease, namely prostate or breast cancer, exemplifying this method for the detection of two transcripts referred to by Ralph et al. as UC331 and UC332, these sequences are RNA encoded by each of two genes (Example 5.6.2 and following, Col. 98). The genes are expressed in blood and non-blood tissues of subjects not having the disease (Col. 101, lines 41-47 and Col. 102, line 5-10). Ralph et al. teach using an oligonucleotide of predetermined sequence which are primers specific to the particular transcripts to detect a presence of the RNA molecules (Col. 98, lines 17-19 and 26-27). Ralph et al. detect a presence in samples from patients having prostate or breast cancer and from healthy volunteers (Col. 98, lines 5-6). Ralph detect the presence of these RNA in DNA-free total RNA from peripheral blood (Col. 98, lines 5-6). DNA-free total RNA from peripheral blood is RNA of a blood samples which have not been fractionated into cell types, and likewise, it is obtained via the lysis of unfractionated cells. Ralph et al. quantify the level of RNA encoded by the genes from both patients having disease and healthy patients, using relative quantitative RT-PCR (Col. 98, line 8). Ralph et al.

determine a difference between the levels of RNA in diseased and control samples, said difference identifying the gene as a marker of said disease (see also line 13 and 22 which state that the RT-PCR independently confirmed the differential expression of the molecules). Thus, the disclosure provided by Ralph et al. anticipates instant claims 17,19, 57, and 58.

Regarding claims 20, 21, 38, and 41 the detecting and quantifying of said RNA is effected by detecting cDNA derived from the RNA, said cDNA being derived from the reverse transcription of RNA (Col. 98, lines 9-10).

Regarding claims 23 and 24, Ralph et al. quantify the control RNA using relative quantitative RT-PCR (Col. 98, line 8).

Regarding claims 28, 29, 31, and 56, Ralph et al. teach quantifying RNA relative to a housekeeping gene (Col. 64, section 4.9.3.3).

Regarding claims 33, the subjects are human (throughout).

Regarding claim 34, the control subjects do not have disease (Col. 98, line 6).

Regarding claim 49, Ralph et al. teach control subjects with different stages of disease (Col. 61, lines 35-40).

Regarding claim 61, Ralph et al. teach that UC331 is widely expressed in many dtissue and cell types, and since it is expressed in many cell types other than blood, it is considered "predominantly expressed in non-blood tissue." Likewise, a sequence search of UC332 (SEQ ID NO: 29 taught by Ralph et al.) revealed that this molecule also appears to be expressed in the adrenal gland, hypothalamus, and lung carcinoma (see results of sequence search available in file record supplemental files). Thus, it is an inherent property of the molecules identified by Ralph et al. that they are expressed predominantly in non-blood tissue.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al. (WO 98/24953) or Ralph et al. (US 6190857) either taken in view of Sharma et al. (WO 98/49342, as cited in IDS).

The teachings of Ralph et al. are set forth previously in this office action.

Regarding claim 43, Ralph et al. teach that their method may be used to discover disease markers for any disease state that affects the peripheral blood leukocytes, including metastatic or organ defined cancer (Col. 9, line 66- Col. 19, line 3). Ralph et al. do not specifically teach that the disease is colorectal cancer.

Sharma et al. teach that "from the very early stages of disease...the whole organism responds to the changed condition" (p. 19, 4th full ¶), and teaches a methods for identifying two or more markers useful for diagnosing a disease by looking for differentially expressed genes in total RNA isolated from whole blood samples (throughout). Sharma et al. particularly teach that a disease in which their method would be useful is cancer of the bowel (p. 6, 2nd ¶).

Therefore, given the teaching of Ralph et al. that their method would be useful for finding markers in organ defined cancers, and the express teaching of Sharma et al. that differentially expressed markers can be identified in the blood for the detection of bowel cancer, it would have been prima facie obvious to modified the methods taught by Ralph et al. so as to have screened

for markers for colorectal cancer as taught by Sharma et al. One would have been motivated to modify the methods taught by Ralph et al. in order to provide markers for a different type of cancer, following the express suggestion of Ralph et al. that their methods could be used to discover disease markers for disease states which include metastatic or organ defined cancer. Thus, in view of the prior art, the claimed invention is prima facie obvious.

15. Claims 17, 19, 20, 21, 23, 24, 28, 29, 31, 33, 34, 38, 41, 43, 56, 57, 58, and 61are rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. (WO 98/49342, as cited in IDS) in view of either Ralph et al. (WO 98/24953) or Ralph et al. (US 6190857).

16. This new grounds of rejection is written to address newly added claim 61. It has been applied to all claims that could be rejected under the combination.

Sharma et al. teach that from the very early stages of diseases the whole organism response to the changed condition (p. 10, 4th full ¶). In light of this, Sharma et al. teach a method for identifying a marker useful for diagnosing a disease comprising the steps of detecting the presence of RNA in an unfractionated sample of whole blood from each of one or more subjects having said disease and quantifying a level of said RNA in said sample. Namely, Sharma et al. teach the preparation of gene transcript patterns beginning with extraction of mRNA from tissues, cells or body parts of an individual or organism which has a disease or condition (p. 7, final ¶, p. 12, 1st ¶), and particularly teach the isolation of mRNA from unfractionated whole blood samples, where unfractionated is interpreted as meaning that the cell types within blood were not separated from one another (p. 35, section 5.1.1). Furthermore, the whole blood samples would contain RNA from leukocytes which have not been fractionated into cell types. Sharma et al. teach quantifying the level of expression and determining a difference

between the quantified level in the sample from the diseased subject and a similarly quantified level of genes of control RNA from an unfractionated sample of whole blood from each of one or more first control subjects (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach that these methods are carried out by producing amplification products from RNA extracted from an unfractionated sample of whole blood (p. 18 and p. 35, Example 5).

Sharma et al. teach that the invention can detect diseases years before other subjective or objective symptoms may appear (p. 11, third full ¶).

Sharma et al. teach that diagnostic patterns can be provided that include markers of disease progression (p. 7, first ¶).

Sharma et al. teach the detection of many genes, including second, third, etc. (p. 16) genes and teach the sampling of more than one diseased and/or control subject to determine quantified levels of expressed markers (p. 21, first full ¶).

Sharma et al. teach detecting RNA by detecting cDNA derived from RNA (p. 18, steps (c) and (d), for example).

Sharma et al. teach quantifying the level of control RNA in said sample (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach isolating the control RNA into bands on an electrophoresis gel for quantification (p. 13).

Sharma et al. teach isolating RNA via extraction prior to the detection step (p. 12).

Sharma et al. teach that the subjects include human subjects (p. 7, 2nd full ¶).

Sharma et al. teach that control subjects should be free of disease (p. 9, first full ¶).

Sharma et al. teach that their methods will result in the selection of between 2 and 1000 probe species for isolation, and that these probes reflect genes which have altered expression in the diseases or conditions in question, or particular stages thereof (p. 16, beginning at line 8).

Sharma et al. do not teach using an oligonucleotide of predetermined sequence or more specifically, primers specific for only RNA and/or cDNA complementary to said RNA, nor do they explicitly teach that the genes isolated are predominantly expressed in said non-blood tissue.

Ralph et al. carry out a very similar differential display method to identify markers of disease in blood and then confirm the differential expression using RT-PCR. Namely, Ralph et al. teach that responses secondary to disease states may be reflected in changing patterns of leukocyte mRNA levels that correlate with the presence of the disease state (Col. 5, lines 27-33). Throughout, Ralph et al. teach a method of identifying differentially expressed markers using RNA fingerprinting, and the techniques used by Ralph et al. include amplification of mRNA using random primers and identifying differentially expressed molecules using gel electrophoresis. Ralph et al. further explicitly teach that "frequently mRNAs identified by RNA fingerprinting or differential display as being differentially regulated turn out not to be so when examined by independent means. It is, therefore, critical that the differential expression of all mRNAs identified by RNA fingerprinting be confirmed as such by an independent methodology (paragraph bridging Col. 98-100)."

Ralph et al. exemplify this confirmation method in Example 5.6.2, beginning in column 98. Ralph et al. teach the use of RT-PCR to identify two or more markers useful for diagnosing a disease, namely prostate or breast cancer, exemplifying this method for the detection of two

transcripts referred to by Ralph et al. as UC331 and UC332, these sequences are RNA encoded by each of two genes (Example 5.6.2 and following, Col. 98).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Sharma et al. so as to have included the RT-PCR step using oligonucleotides of predetermined sequence as taught by Ralph et al. so as to have provided a means to confirm the differential expression of the identified markers. Regarding the requirement that the subject genes are genes that are expressed in blood and non-blood tissue of a subject not having said disease, this is considered to be an inherent property of at least some of the genes that would be detected by the methods taught by Sharma et al. in view of Ralph et al. This is also true of the limitation of newly added claim 61 which requires that the markers are predominately expressed in non-blood tissues. Sharma et al. in view of Ralph et al. are using substantially the same method steps as claimed by applicant, and so the detected transcripts would be expected to include genes expressed in blood and non-blood tissue of a subject not having said disease, as well as genes which are predominately expressed in non-blood tissues.

17. Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. in view of either Ralph et al. as applied to claims 17, 19, 57, and 58 above, and further in view of Wei et al. (Chinese Medical Journal, Volume 106(12):893-897, 1993).

The teachings of Sharma et al. in view of Ralph et al. as they apply to claims 17, 19, 57, and 58 are previously discussed in this office action.

Sharma et al. teach that "the disease or condition may be any condition, ailment, disease or reaction that leads to the relative increase or decrease in the activity of informative genes...

(p. 6, line 1)" and further teach a wide variety of diseases and conditions of various etiologies that are appropriate for the practice of their methods. Further, Ralph et al. teach that their method relies upon detecting a response of circulating leukocytes to the disease state (Col. 5, line 1) and that the detection of an immune response may be reflected in changing patterns of leukocyte mRNA levels that correlate with the presence of the disease state (Col. 5, 27-34).

Neither Sharma et al. nor Ralph et al. teach using their methods for the detection of markers for diabetes, in particular.

Wei et al. teach that insulin dependent diabetes mellitus is a kind of autoimmune disease, and furthermore teach that IL-6 is differentially expressed in the blood of patients having diabetes versus control patients. Thus, Wei et al. exemplify that at least a single differentially expressed molecule is present in the blood of patients having diabetes relative to healthy patients.

Therefore, at the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to have applied the methods taught by Sharma et al. in view of Ralph et al. to the disease diabetes in order to identify additional markers in the blood that would be useful for detecting and understanding this disease. One would have been generally motivated by the teachings of Sharma et al. and Ralph et al. concerning the broad applicability of their methods, and by the teachings of Wei et al. that at least one marker differentially expressed in the blood of patients having diabetes versus healthy patients had been found. Given the teachings of Sharma et al. and Ralph et al. one would have reasonably expected to identify numerous additional markers in RNA extracted from whole blood of the relevant subjects using differential display methods, and then to have confirmed those markers using the RT-PCR

methods taught by Ralph et al. Therefore, in view of the teachings of the prior art, the claimed invention is prima facie obvious.

18. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. in view of either Ralph et al. as applied to claims 17, 19, 57, and 58 above, and further in view of Kasuga et al. (US 6133502).

The teachings of Sharma et al. in view of Ralph et al. as they apply to claims 17, 19, 57, and 58 are previously discussed in this office action.

Sharma et al. teach that "the disease or condition may be any condition, ailment, disease or reaction that leads to the relative increase or decrease in the activity of informative genes... (p. 6, line 1)" and further teach a wide variety of diseases and conditions of various etiologies that are appropriate for the practice of their methods. Further, Ralph et al. teach that their method relies upon detecting a response of circulating leukocytes to the disease state (Col. 5, line 1) and that the detection of an immune response may be reflected in changing patterns of leukocyte mRNA levels that correlate with the presence of the disease state (Col. 5, 27-34).

Neither Sharma et al. nor Ralph et al. teach using their methods for the detection of markers for heart failure, in particular.

Kasuga et al. teach that expression of monocyte chemotactic and activating factor mRNA is known to increase in the blood of acute heart failure patients.

Therefore, at the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to have applied the methods taught by Sharma et al. in view of Ralph et al. to the disease heart failure in order to identify additional markers in the blood that would be useful for detecting and understanding this disease. One would have been generally

motivated by the teachings of Sharma et al. and Ralph et al. concerning the broad applicability of their methods, and by the teachings of Kasuga et al. that at least one marker differentially expressed in the blood of patients having heart failure versus healthy patients had been found. Given the teachings of Sharma et al. and Ralph et al. one would have reasonably expected to identify numerous additional markers in RNA extracted from whole blood of the relevant subjects using differential display methods, and then to have confirmed those markers using the RT-PCR methods taught by Ralph et al. Therefore, in view of the teachings of the prior art, the claimed invention is prima facie obvious.

Double Patenting

19. The previously set forth rejections for obviousness type double patenting are maintained and applied to newly added claims 57-61. Applicant did not provide any arguments particularly traversing these rejections.

Response to Remarks

The previously set forth rejections for indefiniteness and for written description are withdrawn in view of cancellation of the rejected claims.

Applicant traverses the rejections in view of Ralph et al., arguing that Ralph et al. do not teach testing blood samples which have not been fractionated into cell types. Applicant provides a declaration to support their argument. The arguments and the declaration have been considered and are not persuasive.

The reference very clearly states that "DNA-free total RNA from the peripheral blood" was used in their analysis, as cited in the rejection. Applicant is reminded that "A reference may

be relied upon for all that it would have reasonable suggested to one having ordinary skill in the art, including nonpreferred embodiments" and that the art's disclosure of more than on alternative does not constitute a teaching away from any of these alternatives (MPEP 2123).

In this case, applicant is arguing that Ralph et al. may have said "DNA-free total RNA from peripheral blood" but that they didn't mean as much. The declaration provides Mr. Dobner's interpretation of the Ralph et al. references but does not provide any factual evidence to support his interpretation of the references. The conclusion is drawn entirely based on his interpretation of the reference. In the Dobner declaration, paragraphs 1-12 summarize the examiner's position. Beginning in paragraph 13, Dobner sets forth his opinion that the claim limitations are not met by the teachings of Ralph et al. Dobner asserts that carefully following the written description of the Ralph et al reference reveals that the RNA referred to in section 5.6.2 as "DNA-free total RNA" is actually prepared from isolated mononuclear cells. Noteably, there is no direct statement in the disclosure of Ralph et al. to support this assertion. Applicant points to the beginning of Example 6 (Col. 95, section 5.6) where Ralph et al. state that RNA fingerprinting was performed as set forth in section 4.12, and that section 4.12 points to section 4.11.1 where RNA was prepared from nucleated circulating peripheral blood cells. Dobner states that Col. 67, line 46 makes it clear that this RNA was used for both RNA fingerprinting and relative quantitative RT-PCR. This section does not say, however, as Dobner and applicant imply that ALL following examples used the same RNA, and to the contrary, as noted in the rejection, in sections 4.11.3 and 5.6.2 Ralph et al. clearly say that for those particular RT-PCR assays "total RNA from peripheral blood" was used.

Dobner points out in paragraph 17 that the RNA preparation described in 4.11.1 refers back to section 4.9.1 and in this example RNA is isolated from nucleated circulating peripheral cells. This is not disputed. Dobner does not ever point to a direct statement in Ralph where they contradict themselves regarding their very clear language that "DNA-free total RNA from peripherial blood" was used in the confirmation RT-PCR examples where they clearly and directly state that DNA-free total RNA was used. No example that includes this language refers back to other examples where mononuclear cells were isolated, even though Ralph et al. is very careful in many instances throughout their disclosure to point to the mononuclear isolation methods when they were used. This weighs heavily on the side of reasoning that Ralph et al. would have referred back to a mononuclear cell RNA isolation method if the intended to point to such a method. Instead, they make a direct statement of what they did, consistently pointing from section 5.6.2 to 4.11.3, both sections which contain the same language and which contain no further reference to other sections of the Ralph et al. disclosure.

In paragraph 20 Dobner the RNA used for relative quantitative RT-PCR can also be traced back to the method described in 4.9.1, a method in which cells are fractionated with ficoll gradients. Applicant states that this is so based on Ralph et al.'s statement in Col. 67, line 46. This line of Ralph et al. has been addressed previously in this office action, namely, this argument is not persuasive since Ralph et al. do not state in section 4.11.3 nor in 5.6.2 that they used ficoll gradients to isolate RNA and instead state that "total RNA from peripheral blood" was used. Line 46 of column 67 does not state that every RT-PCR assay they completed used the same RNA isolation, nor does it say that those assays that used "total RNA from peripheral

blood" used a ficoll gradient to obtain that RNA (in which case, it is agreed that the RNA would not contain total RNA from peripheral blood).

Dobner admits that there is no specific linkage between the relative quantitative RT-PCR methods in Ralph et al. (WO 98/24935), paragraph 21 of the declaration. Dobner points out that there are explicit references to the expression of markers in peripheral blood leukocytes in the WO disclosure. The statement cited in paragraph 21 does not say what RNA isolation method was used to test mRNA in the peripheral blood leukocytes. Total RNA from peripheral blood would certainly have been a valid means to accomplish the task they set forth in the cited sentence, and, in fact is the means that Ralph et al. expressly state that they used.

In paragraph 22 of the declaration Dobner states that Ralph et al. refer to the mononuclear cells whose RNA they isolated as the "peripheral blood leukocytes" throughout their disclosure. At the time the invention was made, it was common to refer to a ficoll plaque isolation as a means to obtain "peripheral blood leukocytes," and in fact this method does isolate some, if not all peripheral blood leukocytes.

The declaration in paragraphs 23-24 of the declaration rely on those previously set forth which have been addressed and were not persuasive.

Dobner points out that in Col. 98, lines 32-36 that Ralph et al. refer to the steady state abundances of mRNA in "peripheral blood leukocytes " that were identified in RNA fingerprinting, pointing out that the RNA fingerprinting methods disclosed by Ralph et al. used RNA from the isolated mononuclear cell fraction. This is agreed but does not remove the fact that Ralph et al. disclose that the RT-PCR confirmation was completed on "DNA-free total RNA from peripheral blood."

The remainder of the declaration focuses on the fact that other examples in Ralph et al. use RNA prepared from mononuclear cells. Applicant is reminded that "A reference may be relied upon for all that it would have reasonable suggested to one having ordinary skill in the art, including nonpreferred embodiments" and that the art's disclosure of more than on alternative does not constitute a teaching away from any of these alternatives (MPEP 2123).

It is agreed that most of the examples set forth by Ralph et al. teach the use of RNA that was isolated from a mononuclear cell fraction, and the expert opinion provided in the declaration has been given some weight. However, the facts supporting the opinion have been carefully considered and are not persuasive to conclude that when Ralph et al. clearly and explicitly stated that they used "total RNA from the peripheral blood" that they meant something different than what they clearly stated in their disclosure (MPEP 716.01(d)). As previously noted, and as discussed throughout the declaration, Ralph et al. refer back to the mononuclear cell isolation process repeatedly throughout their document, but when they make the direct statement regarding total RNA from the peripheral blood they do not refer back to the mononuclear cell isolation process.

In paragraph 28 and following of the declaration Dobner points out that Ralph et al. refer to differential expression of molecules observed by fingerprinting RNA from the mononuclear fraction as being differential expression in the "peripheral blood." It is agreed that Ralph et al. frequently state that these expression products are differentially expressed in peripheral blood, and this is reasonable as cells whose RNA was tested were isolated from the blood.

It is noted that the declaration did not contain a paragraph numbered 33 and that the paragraph on the top of page 8 is incomplete.

Applicant's arguments rely on similar logic as the declaration, referring in large part to the declaration. They are not persuasive for the reasons discussed as to why the arguments in the expert declaration were not persuasive. Applicant states on the sixth page of the remarks that "The fact that the same RNA is utilized for both RNA fingerprinting and relative quantitative RT-PCR is consistently taught throughout the specification." This is not persuasive since Ralph et al. clearly use different and distinct language to describe the RNA used in examples 5.6.2 and 4.11.3. As noted previously neither of these examples externally refer- that is they do not refer to any other examples, and they state clearly and unequivocally that the RNA used in these experiments was total blood RNA.

The declaration and arguments based thereupon are not persuasive and the rejection is maintained even in view of these.

Applicant argues that Sharma et al. teach away from using "sequence based methods," citing the Examiner's assertion in a previous office action. However, this is not persuasive. Sharma et al. cannot be construed as always teaching away from any possible application of sequence based methods. The examiner's statement was in regard to a modification of the initial "marker finding" methods used by Sharma et al., and Ralph et al. carry out a very similar differential display method to identify markers and then confirm the differential expression using RT-PCR. Sharma et al. does not teach away from confirming the differential expression that they observe by use of sequence based methods. The relevance of the Ralph et al. reference only came to light after the original statements by the examiner in the previous office action. Sharma et al. do not teach away from the methods of Ralph et al., in fact the differential display techniques referred to by Ralph et al. as "RNA fingerprinting" are almost identical to the

techniques used by Sharma et al. Ralph et al. further explicitly teach that "Frequently mRNAs identified by RNA fingerprinting or differential display as being differentially regulated turn out not to be so when examined by independent means. It is, therefore, critical that the differential expression of all mRNAs identified by RNA fingerprinting be confirmed as such by an independent methodology (paragraph bridging Col. 98-100)."

Applicant further argues that Ralph et al. does not demonstrate nor suggest a method which uses RNA of blood samples which have not been fractionated into cell types, as required by claim 43. These arguments have not been found persuasive. Even if they were, Sharma et al. clearly exemplifies such methods (Col. 18) for the identification of differentially expressed markers in disease. The rejection is maintained.

New grounds of rejection are added in this office action to address newly added claims.

Conclusion

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is

(571)272-0507.

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Juliet C. Switzer
Primary Examiner
Art Unit 1634

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